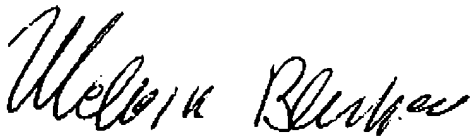

Dr. Melvin Blecher
Attorney-at-Law
Registration No. 33,649

Law Offices of Dr. Melvin Blecher
4329 Van Ness St., NW
Washington, DC 20016-5625
Tel: 202 363 3338/0373
FAX: 202 362 8404
e-mail: MBiplaw@comcast.net

Proteoglycan

Glycoaminoglycans (GAG's)

These are long unbranched PS chains composed of repeating disaccharide units, and are called GAG's because one of the two sugars is always an amino sugar e.g. N-acetylglucosamine (GlcNac). GAG are highly negatively charged due to the presence of sulphate or carboxyl groups or both on many of the sugar residues. There are seven types of GAG distinquished by:

(a) the various sugar residues,

(b) type of linkage between the sugar residues,

(c) number and location of sulphate residues.

They are: hyaluronic acid (only one not sulphated) chondriotin-4-sulphate, chondroitin-6-sulphate, dermatan sulphate, heparan-sulphate, keratan-sulphate and heparin.

Hyaluronic acid (HA) is the odd one with no sulphate, and it is a very long chain of up to 2200 sugars long with *Mr* from 4000 to 8 million. The

other GAG's are much smaller around 300 sugar residues with *Mr* from 8,000 to 30,000. In addition the others have extra sugars such as xylose and galactose, which serve to provide a covalent link to protein. HA has no other sugars and does not covalently link to protein, but does have non-covalent links.

In the body these complex PS may be used on their own to thicken body fluids and provide lubricating fluids. However, the body has more sophisticated requirements, and uses these GAG's in higher order structures such as in the formation of complex proteoglycan.

As mentioned earlier disaccharide units have extra sugars for linking to protein so protein-PS complex is formed called proteoglycan (PG) in which the major component is PS and the minor is protein. Major use of PG in the body is as the ground matrix, which embeds the tissue proteins collagen and elastin of skin and bone.

Properties of tissue depend on the ratio of PG to proteins collagen/elastin e.g. in children less PG more collagen and skin is soft. In adults more PG less collagen makes the skin tough/less soft. People

over 50 years have much less collagen and much more PG so skin is very tough.

Alot of research focused on the mechanism of the change and the enzymes involved. If it can be identified and inhibited so skin stays soft then there is a fortune to be made. Cosmetic preparations containing collagen or essential amino acids applied onto the skin have no effect on collagen synthesis.

Cartilage

Consider cartilage PG, this is the tough rubbery material located between bones to prevent grating of bones together. Cartilage is composed of collagen and PG.

The PG consists of a long spine of hyaluronic acid and attached to the spine non-covalently are protein chains and attached to the protein chains are GAG's chondroitin sulphate (CDS) and keratan sulphate (KTS). Protein core is normally 1900 amino acids long with as many as 100 CDS and 60 KTS chains attached and each GAG chain has up to 50 disaccharide units.

CDS repeating unit is GalNac-GlcUA with an alternating beta(1-3) beta(1-4) arrangement. The

beta-link would tend to promote fibre formation as in cellulose, but this is prevented by the strong charges from the sulphate and the carboxyl groups, which cause repulsion between the chains.

So GAG chains are long and straight, and spaced out by repulsion to give a 'bottle-brush' structure. The chains are not static, but are free to sweep through the solution trapping large quantities of water by H-bonding to the sugar residues through the OH groups. Thus a gel is formed, which can resist pressure.

The GAG are joined covalently to the protein core, and this involves the extra sugars xylose and galactose, normally linked through the OH of a serine residue on the protein.

As many as 100 PG chains are attached to hyaluronic acid though not covalently but by ionic interactions or salt bridges. This involves special link proteins to form a bridge between PG chain and HA.

Clearly complicated arrangement, but under intensive study because these structures are at the heart of one of the most wide spread scourges of our

time, and that is **arthritis.**

Arthritis is simply inflammation of the joints between bones, but is very painful and it is clear from research that arthritis involves changes to cartilage PG.

What causes the changes, and what are the changes?

Answers to these questions are needed to understand the process of degeneration in arthritis.

For more detail on this topic see the text book pages 409-412

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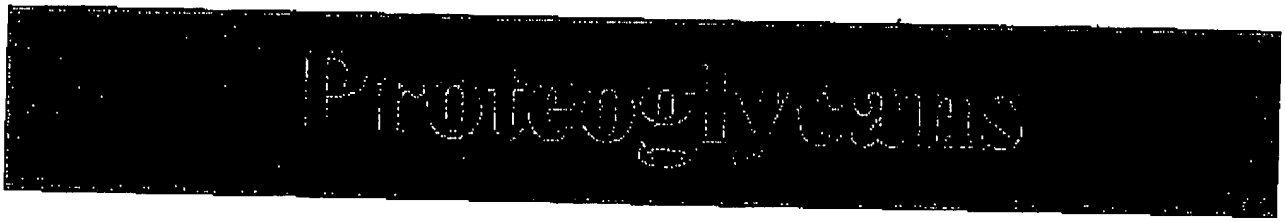
Starch	Cellulose	Gelling PS	Agarose
Glossary			

PROTEOGLYCANS



General proteoglycan issues

- What is a Proteoglycan? and how does it differ from a glycoprotein?
- Proteoglycan nomenclature
- What are the roles of proteoglycans
- Tissue specific expression of proteoglycans

Specific proteoglycan types

- Neural proteoglycans
- Basement membrane proteoglycans
- Collagens that are also proteoglycans
- Small leucine rich proteoglycans
- Aggrecan
- Chondroitin sulphate proteoglycans
- Keratan sulphate proteoglycans
- Heparin sulphate proteoglycans
- Other proteoglycans

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What is a Proteoglycan?

- What is a Proteoglycan? and how does it differ from a glycoprotein?
- What is the role of glycosylation

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Proteoglycan nomenclature

As with all areas of science nomenclature is important, and never more so than when a field is expanding in the way that the proteoglycan and glycosaminoglycan fields are. The historical rational behind the nameing of proteoglycans, and the reasons some workers want a reappraisal of proteoglycan and glycosaminoglycan nomemclature are examined.

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What are the roles of proteoglycans

Many new functions are being ascribed to proteoglycans. Some of these are examined

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Bio-synthetic pathways

The bio-synthesis of proteoglycans and the glycosaminoglycan chains attached is examined.

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Tissue specific expression of proteoglycans

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Neural proteoglycans

Several proteoglycans have been identified which appear to be unique to neural tissues. These are examined here.

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Basement membrane proteoglycans

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Collagens that are also proteoglycans

There is a group of collagens termed FACIT collagens, which are each glycosylated by chondroitin sulphate.

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Small leucine rich proteoglycans

This is a group of small interstitial proteoglycans which have a high degree of homology in their protin core sequence. Each has between 10 and 12 highly conserved leucine rich tandem repeats which makes up the central portion of the core protein. The current members of the group are fibromodulin and lumican, which are both keratan sulphate substituted, and decorin and biglycan which are both chondroitin sulphate substituted.

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CS proteoglycans

There are a large number of proteoglycans which are exclusively glycosylated by chondroitin sulphate

- Versican
- Decorin
- Biglycan

And also aggrecan, which is predominantly glycosylated by chondroitin sulphate but does have some keratan sulphate.

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KS proteoglycans

There are a few proteoglycans which are glycosylated exclusively by keratan sulphate:

- Fibromodulin
- Lumican

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HS proteoglycans

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Aggrecan

Aggrecan is the large cartilage specific aggregating proteoglycan . It is one of the princliple components of cartilage, and is responsible for many of its properties. Heavily glycosylated with chondroitin sulphate it interacts with hyaluronic acid to form a huge aggregate. The interaction is stabilised by link protein .

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Other proteoglycans

The proteoglycan field is changing rapidly, many new proteoglycans being identified, and proteins which have been isolated are being found to be proteoglycans. This